CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213871
PDUFA Goal Date	06/25/2021
OSE RCM #	2020-1837
Reviewer Name(s)	Lindsey W. Crist, Pharm.D., BCPS
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Team Leader	Jacqueline Sheppard, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	January 7, 2022
Subject	Evaluation of Need for a REMS
Established Name	Abrocitinib
Trade Name	Cibinqo
Name of Applicant	Pfizer, Inc
Therapeutic Class	Janus Kinase (JAK) 1 Inhibitor
Formulation(s)	Oral tablet (50 mg, 100 mg, and 200 mg)
Dosing Regimen	100 mg by mouth daily • If an adequate response is not achieved with Cibinqo 100 mg orally daily after 12 weeks, consider increasing dosage to 200 mg orally once daily. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Cibinqo (abrocitinib), is necessary to ensure the benefits outweigh its risks. Pfizer, Inc submitted a New Drug Application (NDA) 213871 for abrocitinib with the proposed indication: (b) (4) The Applicant did not submit a proposed REMS or risk management plan with this application. The Applicant's proposed labeling includes a Boxed Warning for serious infections, malignancy, and thrombosis and a Medication Guide.

DRM and the Division of Dermatology and Dentistry (DDD) agree that a REMS is not needed to ensure the benefits of abrocitinib outweigh its risks. The benefit of abrocitinib for the treatment of moderate-to-severe atopic dermatitis was demonstrated in two phase 3, placebo-controlled trials (B7451012 and B7451013) which showed both abrocitinib 100 mg and 200 mg were statistically superior to placebo for the co-primary endpoints at 12 weeks. However, safety issues are increased with the abrocitinib 200 mg dose compared to the 100 mg dose.

The risks associated with abrocitinib include serious infections, malignancies, thrombosis, major adverse cardiovascular events (MACE), hematologic abnormalities (e.g., thrombocytopenia and lymphopenia), and retinal detachment.

Based on the overall benefit/risk assessment of abrocitinib and recent post-market evidence showing increased safety issues with the JAK inhibitor class, the review team recommends changes to the proposed indication and dosing. Although a higher treatment effect for abrocitinib 200 mg was observed in trials, the review team concluded the higher dose is limited by the safety profile. The 200 mg dose will be reserved for patients with refractory atopic dermatitis who have an inadequate response to 100 mg. (b) (4) Furthermore, the clinical reviewer recommends limiting the indication to third-line (refractory) atopic dermatitis based on the overall safety issues with the JAK inhibitor class. This recommendation is consistent with the JAK inhibitors place in therapy for other inflammatory conditions.

The Agency's revised indication and dosage recommendations are as follows:

- Cibinqo is indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics or when use of those therapies is inadvisable
- The recommended dosage of Cibinqo is 100 mg orally once daily.
    - If an adequate response is not achieved with Cibinqo 100 mg orally daily after 12 weeks, consider increasing dosage to 200 mg orally once daily. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.

The labeling for abrocitinib will communicate the risks of serious infections, mortality, malignancies, MACE, and thrombosis with a Boxed Warning. This Boxed Warning is consistent with the recently updated Boxed Warnings for other agents in the JAK inhibitor class approved for inflammatory conditions including atopic dermatitis. The risk of laboratory abnormalities (including hematologic abnormalities) will be communicated in Section 5, Warnings and Precautions and Section 2, Dosage and Administration which includes a recommended schedule for monitoring complete blood counts (CBC) and recommendations for discontinuation of therapy based on CBC results. The risk of retinal detachment will be communicated in Section 6, Adverse Reactions. Labeling will also include a Medication Guide to communicate risks to patients. The likely prescribing population may also be familiar with many of the risks (e.g., infections, malignancy, hematologic abnormalities) and appropriate management as they are similar to risks associated with conventional immunosuppressants used for treatment of moderate-to-severe atopic dermatitis.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Cibinqo (abrocitinib) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 213871 for abrocitinib with the proposed indication (b) (4) The Applicant did not submit a proposed REMS or risk management plan with this application. The Applicant's proposed labeling includes a Boxed Warning for serious infections, malignancy, and thrombosis and a Medication Guide to convey risks to patients. This application is under review in the Division of Dermatology and Dentistry (DDD).

2 Background

2.1 PRODUCT INFORMATION

Cibinqo (abrocitinib), a new molecular entity[a], is a selective Janus kinase (JAK) 1 inhibitor proposed for (b) (4) [1] Abrocitinib is proposed to be available as an oral tablet (50 mg, 100 mg, and 200 mg). The Applicant's proposed dosing regimen is 100 mg or 200 mg by mouth daily based on individual goal of therapy and potential risk for adverse reactions.[2] Abrocitinib is likely to be administered primarily in the outpatient setting for the chronic treatment of atopic dermatitis.[b] Abrocitinib is not currently approved in any jurisdiction.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

If approved, abrocitinib will be the sixth JAK-inhibitor approved in the United States. While the JAK inhibitors do not currently have a REMS, risk mitigation strategies for the communicating the risks of the JAK inhibitor class has evolved over time. Xeljanz (tofacitinib) was originally approved on November 6, 2012 for the treatment of moderate to severe active rheumatoid arthritis with a REMS that was comprised of a Medication Guide and Communication Plan (CP) to mitigate the risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, and low blood cell counts. The REMS was eliminated in February 2016 after the Agency determined that it was no longer necessary because the activities had been completed and the most recent REMS assessment demonstrated the CP REMS had met its goals.[3,4]

Based on data received from postmarketing studies of tofacitinib and the issuance of a Safety Labeling Change Notification Letter, labeling for the JAK inhibitors approved for inflammatory conditions was revised in December 2021.[5-10] The safety labeling changes were primarily based on data from postmarketing studies for tofacitinib; however, the Agency determined these risks to be a class effect for JAK inhibitors approved for inflammatory conditions. The Boxed Warnings and Warning/Precautions sections for these agents were revised to include information about the risk of major adverse cardiovascular events (MACE), malignancy, thrombosis, and mortality. Additionally, the indications were revised to limit use to patients who have an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers. Opzelura (ruxolitinib cream) was approved for the treatment of atopic dermatitis in September 2021 with a Boxed Warning for serious infections, mortality, malignancies, MACE, and thrombosis similar to the boxed warning for JAK inhibitors approved for other inflammatory conditions. See Appendix 10.2 for a table of approved JAK inhibitors.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213871 relevant to this review:

- **02/17/2018:** Breakthrough Therapy Designation granted for abrocitinib (PF-04965842 tablets) for the treatment of atopic dermatitis under IND 123554.
- **08/25/2020:** NDA 213871 submission for abrocitinib for the treatment of moderate-to-severe atopic dermatitis received.
- **12/08/2020:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, determination of the necessity of a REMS for the application remained under review for abrocitinib.[11]
- **03/02/2021:** A Late-Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that labeling, including a Boxed Warning, in addition to routine pharmacovigilance, would be adequate risk management for abrocitinib. A REMS was not currently planned.[12]

- **04/06/2021:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date by 3 months due to the 120-day safety update which included data from an additional phase 3 clinical study, B7451036.

- **08/23/2021:** The Agency issued a Safety Labeling Change Notification Letter to the sponsors of JAK inhibitors approved for inflammatory conditions, Xeljanz (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib). Labeling changes included updates to the Boxed Warning to include information about the risk of major adverse cardiovascular events (MACE), malignancy, thrombosis, and mortality. The indications were revised to restrict JAK inhibitor use to patients who have refractory disease that cannot be adequately controlled with other agents, including biologics or when other agents are inadvisable. These safety changes were based on a post-marketing study for tofacitinib and the collective experience with safety of this class.[5-7,13]

- **09/01/2021:** The Agency issued a Drug Safety Communication to communicate the required safety labeling changes for JAK inhibitors for chronic inflammatory conditions.

- **12/02/2021:** The Agency approves labeling supplements submitted in response to the Safety Labeling Change Notification Letter for Xeljanz (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib).[8-10]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Atopic dermatitis, commonly known as eczema, is an inflammatory skin condition characterized by pruritis, erythema, eczematous lesions (crusting, serous oozing, and blister formation), dry skin, and lichenification.[14] The pathogenesis is complex and involves multiple factors, including skin barrier abnormalities, genetics, immune dysregulation and inflammation, altered skin microbiome, and environmental triggers.[14] Atopic dermatitis may be associated with other immunoglobulin E (IgE) associated diseases including acute allergic reactions to food, asthma, urticaria, and allergic rhinitis.

The onset of atopic dermatitis occurs by age 1 in 60% of patients and by age 5 in 90%.[15] Atopic dermatitis follows a chronic, relapsing course over months to years. Atopic dermatitis persists into adulthood in about 10 to 30% of cases.[15] The severity of atopic dermatitis and its effect on quality of life and psychosocial well-being varies across patients. There is not a gold standard for measurement of disease severity and several scales are utilized in clinical trials and practice.[15] The National Institute for Health and Care Excellence (NICE) has developed the following practical guide to address the severity of atopic dermatitis:[16,c]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

- Mild – Areas of dry skin, infrequent itching (with or without small areas of redness); little impact on everyday activities, sleep, and psychosocial well-being.
- Moderate – Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening); moderate impact on everyday activities and psychosocial well-being, frequently disturbed sleep.
- Severe – Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation); severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep.

In the United States, the prevalence of childhood atopic dermatitis ranges from 8-16%.[14,17] An estimated 16.5 million adults in the United States have atopic dermatitis with reported prevalence ranging from about 1-7%.[14,17-20,d] About 40% of adults with atopic dermatitis report moderate-to-severe disease.[18]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Non-pharmacologic treatment for atopic dermatitis includes elimination of exacerbating factors, maintaining skin hydration, and appropriate bathing practices.[16] Exacerbating factors may include low-humidity environments, emotional stress, dry skin, overheating of skin, and exposure to solvents and detergents. Phototherapy may be considered in those with diffuse pruritis that is not controlled with topical therapy alone.

The FDA-approved pharmacologic treatment options for atopic dermatitis include corticosteroids, topical calcineurin inhibitors (e.g., tacrolimus ointment and pimecrolimus cream), a topical phosphodiesterase-4 (PDE-4) inhibitor (crisaborole ointment), a topical JAK-inhibitor (ruxolitinib cream), and an interleukin-4 (IL-4) receptor alpha antagonist (dupilumab injection) [See Appendix 10.3, Table 2].

Treatment selection depends on severity, patient factors, and the safety profiles of the agents. Topical corticosteroids are often the first-line treatment for atopic dermatitis in all age groups, particularly for mild-to-moderate disease. The potency of the topical corticosteroid is guided by the patient's age, body area involved, and degree of skin inflammation. Local adverse events may include burning, stinging, redness, irritation, and skin atrophy. There may be systemic absorption leading to systemic toxicities. Topical calcineurin inhibitors are also indicated for the treatment of atopic dermatitis in pediatric patients ages 2 and older for mild-to-moderate atopic dermatitis (pimecrolimus) or moderate-to-severe atopic dermatitis (tacrolimus). The topical calcineurin inhibitors are labeled as second line options if topical corticosteroids have failed or cannot be tolerated. Labeling for these agents includes a Boxed Warning describing that long-term safety has not been established, and there have been rare cases of malignancy specifically lymphoma and skin cancer. Crisaborole, a topical PDE-4 inhibitor, may also be used in mild-to-moderate atopic dermatitis. It has mild adverse effects (burning and stinging at the injection site) and limited systemic exposure.[16] The newest topical option approved in 2021 for mild-to-moderate atopic dermatitis is Opzelura (ruxolitinib cream), a topical JAK-inhibitor. It is approved for short term, noncontinuous use only. Labeling includes the Boxed Warning for serious infections,

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

mortality, malignancies, MACE, and thrombosis, which is consistent with the other JAK inhibitors approved for inflammatory conditions.

Moderate-to-severe atopic dermatitis may require systemic immunomodulatory therapy to achieve adequate disease control.[21] Dupixent (dupilumab), an interleukin-4 (IL-4) receptor alpha antagonist was approved in 2017 for the treatment of patients ages 6 and older with moderate-to-severe atopic dermatitis. It can be used with or without topical corticosteroids. It is administered as a subcutaneous injection and risks include hypersensitivity, conjunctivitis, and keratitis. The use of systemic corticosteroids is not recommended for long-term management because of an overall unfavorable benefit-risk profile. Adbry (tralokinumab-ldrm) was approved on December 27, 2021 and is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adbry can be used with or without topical corticosteroids. It is administered as a subcutaneous injection and risks are similar to Dupixent. Other conventional immunosuppressant agents (e.g., cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine) have been used off-label to treat atopic dermatitis; however, reported efficacy varies and use is limited by their significant safety profiles, including serious infections, hematologic abnormalities, malignancies (see Appendix 10.4, Table 3). There is an unmet need for additional options for the treatment of moderate-to-severe atopic dermatitis.

4 Benefit Assessment

The efficacy of abrocitinib as monotherapy for the treatment of atopic dermatitis was demonstrated in two Phase 3 studies, B7451012 (NCT 03349060) and B7451013 (NCT03575871).[e] These studies were monotherapy, randomized, double-blind, placebo-controlled, parallel group studies in adolescents (12 years and older) and adults with moderate-to-severe atopic dermatitis. Subjects were randomized to either abrocitinib 100 mg by mouth daily (Study B7451012: N=156; Study B7451013: N=158), abrocitinib 200 mg by mouth daily (Study B7451012: N=154; Study B7451013: N=155), or placebo (Study B7451012: N=77; Study B7451013: N=78). Study drug was administered for 12 weeks. Adolescents represented 15.9% of the population in the monotherapy studies.

The co-primary efficacy endpoints were:

- Proportion of subjects with Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) (IGA 0/1) with a reduction of ≥2 points at Week 12
- Proportion of subjects with at least 75% reduction in Eczema Area and Severity Index (EASI) score from baseline (EASI 75) to Week 12

The Agency noted in the advice letter dated 2/15/2018 that while the planned co-primary endpoints based on the IGA and EASI are acceptable, the Agency considers the IGA endpoint to be the main

[e] An additional phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, phase 3 trial (B7451029, NCT03720470) evaluated abrocitinib in combination with background topical therapy in adults with moderate-to-severe atopic dermatitis. This study provided supportive efficacy and safety data.

primary endpoint.[22]

In Study B7451012, the proportion of subjects with an IGA score of 0 or 1 was 43% for abrocitinib 200 mg, 24% for abrocitinib 100 mg, and 8% for placebo. The proportion of EASI 75 responders was 62% for abrocitinib 200 mg, 40% for abrocitinib 100 mg and 12% for placebo. In Study B7451013, the proportion of subjects with an IGA score of 0 or 1 was 38% for abrocitinib 200 mg, 28% for abrocitinib 100 mg, and 9% for placebo. The EASI 75 responder was 61% for abrocitinib 200 mg, 44% for abrocitinib 100 mg and 10% for placebo.[23] Both abrocitinib doses (100 mg and 200 mg) were statistically superior to placebo for the co-primary endpoints at Week 12 in these studies.[f] A higher treatment effect was observed in the 200 mg dose compared to the lower 100 mg dose in both studies.[23]

In pre-submission meetings, the Agency recommended the Applicant include at least 750 subjects exposed to the to-be-marketed drug product for at least 1 year and of those, that 225 (30%) of the safety population be adolescents (12 years to < 18 years of age) for adequate benefit/risk analysis.[23] The Applicant's adolescent population was less than what the Agency requested. The clinical reviewer concluded that there was not sufficient experience in adolescents (ages 12 years to less than 18 years) to allow an adequate benefit/risk analysis.[23] The Applicant submitted additional data on adolescents from the completed Phase 3 clinical trial, B7451036 with the 120-day Safety Report; however, this data will not be reviewed this review cycle.

The clinical reviewer concluded the Applicant provided adequate evidence of efficacy for the use of abrocitinib in adult subjects (18 years and older) with moderate-to-severe atopic dermatitis.[23] The clinical reviewer's recommendations for the final indication and dosing for approval were based on the overall benefit/risk analysis (see Section 8).

5 Risk Assessment & Safe-Use Conditions

Overall, 2856 subjects with moderate-to-severe atopic dermatitis were treated with abrocitinib in the clinical development program. There were 606 subjects with more than 1 year of abrocitinib exposure.

The Agency's clinical review of safety consisted of the data from the following safety pools:

- All-exposure pool which included a total of 2856 subjects from six studies: the two monotherapy studies, B7451012 and B7451013; Study B7451029 (combination study); Study B7451006 (dose-ranging study); Study B7451014 (randomized withdrawal study), and Study B7451015 (long-term extension study)
- Placebo-controlled safety pool which included a total of 1540 subjects from four studies: B7451012, B7451013, B7451029, and B7451006
    - Of the population, 1198 subjects were exposed to abrocitinib (N=608 for abrocitinib 100 mg daily and N=590 for abrocitinib 200 mg daily) and 342 to placebo
    - Adolescent population accounted for 8.1% (124/1540) of the population and 99 subjects were considered evaluable

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The review team also compared the safety of abrocitinib 100 mg daily dose to the 200 mg daily dose.

The most common adverse reactions (≥1%) associated with abrocitinib are nasopharyngitis, nausea, headache, herpes simplex, increased blood creatinine phosphokinase, dizziness, urinary tract infection, fatigue, acne, vomiting, impetigo, oropharyngeal pain, hypertension, influenza, gastroenteritis, dermatitis contact, herpes zoster, and thrombocytopenia.[24]

The serious adverse events (referred to as risks) determined to be associated with abrocitinib include serious infections, malignancy, thrombosis, major adverse cardiovascular events (MACE), and hematologic abnormalities (e.g., thrombocytopenia and lymphopenia), and retinal detachment.[g] In general, the safety issues are increased with the abrocitinib 200 mg dose compared to the 100 mg dose. These risks in addition to deaths and retinal detachment are discussed below.

5.1 DEATHS

There were four deaths in the clinical studies of abrocitinib for atopic dermatitis. One subject with a history of aortic sclerosis and calcification experienced a serious adverse event (SAE) of sudden death 22 days after discontinuation of study drug (adjudicated as a cardiovascular/cardiac death). The second subject tested positive for COVID-19 infection on Study Day 84, was hospitalized, then died on Study Day 107. The third subject died 7 months after discontinuation from the study due to gastric adenocarcinoma. The fourth subject experienced a SAE of cardiac failure/cardiac insufficiency on Day 334 (study drug had been interrupted on Day 322). These events were determined to be unrelated to study drug by the clinical investigators. The clinical reviewer concluded that none of the deaths established a causal relationship with abrocitinib.[23]

5.2 SERIOUS INFECTIONS

Serious infections leading to hospitalization and death have occurred in patients receiving JAK inhibitors. In the PC safety pool for abrocitinib, serious infections including herpes simplex, herpes zoster, and pneumonia occurred in 6 subjects receiving abrocitinib 100 mg, 2 subjects receiving abrocitinib 200 mg, and 2 subjects receiving placebo. Additionally, TEAEs of herpes simplex occurred in 25 (4.2%) subjects treated with abrocitinib 200 mg daily and in 20 (3.3%) of subjects treated with abrocitinib 100 mg daily compared to 6 (1.8%) subjects on placebo. The clinical reviewer concluded there is a clear dose-related increase in opportunistic infections of herpes associated with abrocitinib. Future long-term studies will be needed to evaluate other serious and opportunistic infections while on JAK inhibitors.[23] The proposed label for abrocitinib includes a Boxed Warning for serious infections with the recommendation to avoid use in patients with active, serious, chronic, or recurrent infections. If a serious infection develops, abrocitinib should be discontinued and the infection controlled.[24]

5.3 MALIGNANCY

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Lymphoma and other malignancies have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. In the placebo-controlled trial 16-week period, malignancy was reported in 1 subject treated with abrocitinib 200 mg and no patients treated with abrocitinib 100 mg or placebo. Across all clinical trials (including the long-term extension), there were 6 adjudicated cases of all malignancies (4 subjects in the abrocitinib 100 mg group and 2 subjects in the 200 mg group).[23] There were 4 adverse events of potential malignancy in the clinical database (2 events of prostate cancer and 2 events of ovarian neoplasm). Additionally, one subject experienced an adverse of event of gastric adenocarcinoma (See Section 5.1, Deaths). The clinical reviewer commented, "It is difficult to make a causal connection of cancer to the drug product currently. A long-term study is needed to evaluate the immunogenicity of abrocitinib on cancer events."[23] The proposed label for abrocitinib includes malignancy in the Boxed Warning with the recommendation to carefully consider the risks and benefits of abrocitinib treatment prior to initiating treatment in patients with known malignancy.[24]

5.4 THROMBOSIS

Thrombosis, including arterial thrombosis, deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors. In the all-exposure group, SAEs of PE and DVT occurred in 3 subjects and 2 subjects, respectively (all receiving abrocitinib 200 mg daily). No thrombosis occurred in subjects receiving abrocitinib 100 mg daily. The clinical reviewer concluded that although a clear connection cannot be made, abrocitinib 200 mg daily was the causal dose in all the adverse events of PE and DVT.[23] The proposed label for abrocitinib includes thrombosis in the Boxed Warning with recommendations to closely monitor patients at high risk for thrombosis and to discontinue treatment if clinical features occur.[24]

5.5 MAJOR ADVERSE CARDIOVASCULAR EVENTS

In the all-exposure pool, three SAEs suggested a MACE event which included two events of myocardial infarction (abrocitinib 200 mg) and one event of sudden death (abrocitinib 100 mg).[23] These events occurred 3 to 6 months after initiation of abrocitinib in subjects older than 60 years with pre-existing cardiovascular risk factors. The investigator determined all three SAEs were unrelated to the study drug. These events were confirmed during adjudication.[23] The proposed label for abrocitinib includes MACE in the Boxed Warning.[24]

5.6 HEMATOLOGIC ABNORMALITIES - THROMBOCYTOPENIA AND LYMPHOPENIA

Dose-related decreases in platelet counts and lymphocytes occurred in the PC safety population in subjects treated with abrocitinib. Adverse events of thrombocytopenia occurred in 1.5% (9/590) of the subjects treated with abrocitinib 200 mg daily compared to no events occurring in those receiving abrocitinib 100 mg or placebo.[h] The clinical reviewer concluded that "thrombocytopenia appears dose-

[h] Of note, Section 6 of the label also states that in all 5 clinical trials, including the long-term extension trials, 6 subjects treated with abrocitinib 200 mg had adverse reactions of thrombocytopenia. The clinical reviewer and statistical reviewer confirmed this number to also be accurate as it was defined differently and included subjects with thrombocytopenia and confirmed platelet counts of less than 75,000/mm^3 (*Source: Email Communication on January 7, 2022*)

response and the higher abrocitinib 200 mg daily dose clearly shows a reduction of platelet count" and notes that platelets appear to recover with continued treatment.[23] The clinical reviewer concluded there was a dose-response reduction in lymphocytes with increasing dose.[23] A higher percentage of subjects in the abrocitinib 100 mg (18.5%) and abrocitinib 200 mg (20.8%) QD groups had an absolute lymphocyte counts $<1\times10^3/mm^3$ compared with the placebo group (11.9%). Hematologic abnormalities are known risks of JAK inhibitors. Thrombocytopenia and lymphopenia is addressed in the proposed label for abrocitinib under Section 5, Warnings and Precautions and Section 2.5 which conveys CBC monitoring recommendations and discontinuation recommendations for platelets < 50,000 mm^3.[24]

5.7 ADVERSE EVENT OF SPECIAL INTEREST

5.7.1 Retinal Detachment

In the all-exposure group, three SAEs of retinal detachment occurred in subjects receiving abrocitinib 100 mg daily (N=2) and abrocitinib 200 mg daily (N=1). The clinical investigator determined the SAEs of retinal detachment were unrelated to abrocitinib. DDD requested an ophthalmology consult to review the cases of retinal detachment. The consulting ophthalmologist concluded, "For two of the reports, it is more likely that severe eye rubbing was the cause of the retinal detachments than the drug product. For the third case, it is likely that the patient's previous cataract surgery was a major factor in the development of the retinal detachment. At this time, it is unlikely that the drug product is a significant cause of retinal detachments."[25] However, the clinical reviewer believes that although the relationship to abrocitinib is not clear and this risk was not observed with JAK inhibitor treatment in RA patients, the atopic dermatitis population is particularly at risk for retinal detachment. Thus, the clinical reviewer recommends retinal detachment be added to labeling.[23] In the abrocitinib proposed label, the three cases of retinal detachment reported in the placebo-controlled trials are described in Section 6, Adverse Reactions.[24] Final labeling negotiations are ongoing.

6 Expected Postmarket Use

Abrocitinib will most commonly be prescribed and self-administered in the outpatient setting. The likely prescribers include primary care providers and dermatologists who are experienced with managing patients with atopic dermatitis. If approved, abrocitinib would be the sixth JAK inhibitor available and the first oral JAK inhibitor approved for moderate-to-severe atopic dermatitis. Ruxolitinib, a topical JAK inhibitor indicated for mild-to-moderate atopic dermatitis, was approved in September 2021. Risks of abrocitinib are similar to ruxolitinib topical cream. Additionally, other agents used for the treatment of atopic dermatitis (e.g., conventional immunosuppressants) share similar risks; therefore, healthcare providers who are likely to prescribe abrocitinib may be familiar with the risks.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and pharmacovigilance for abrocitinib. As part of the abrocitinib pharmacovigilance plan, a non-interventional study collecting real-world data from routine clinical care is being proposed to actively monitor the safety events of interest associated with exposure to abrocitinib in the post-approval setting.[26]

8 Discussion of Need for a REMS

Atopic dermatitis is a common chronic, inflammatory skin condition in the United States. Moderate-to-severe atopic dermatitis negatively impacts activities of daily living, psychosocial functioning, and sleep. While mild atopic dermatitis is often treated successfully with non-pharmacologic treatment and topical corticosteroids, moderate-to-severe atopic dermatitis may require systemic immunomodulatory therapy to achieve adequate disease control. There are limited agents approved for moderate-to-severe atopic dermatitis. If approved, abrocitinib could be an additional treatment option.

The benefit of abrocitinib for the treatment of moderate-to-severe atopic dermatitis was demonstrated in two phase 3, placebo-controlled trials (B7451012 and B7451013) which evaluated treatment with abrocitinib 100 mg, abrocitinib 200 mg compared to placebo in adults and adolescents. Both abrocitinib 100 mg and 200 mg doses were statistically superior to placebo for the co-primary endpoints at 12 weeks in both studies. However, safety issues are increased with abrocitinib 200 mg dose compared to the 100 mg dose. The risks associated with abrocitinib include serious infections, malignancies, thrombosis, MACE, hematologic abnormalities, and retinal detachment.

Abrocitinib was originally submitted with the proposed indication: (b) (4) However, based on the overall benefit/risk analysis of abrocitinib and recent post-market evidence showing increased safety issues with the JAK inhibitor class, the clinical reviewer recommends changes to the proposed indication and dosing.[23] Although a higher treatment effect for abrocitinib 200 mg was observed in trials, the clinical reviewer concluded the higher dose is limited by the safety profile. The 200 mg dose will be reserved for patients with refractory atopic dermatitis who have an inadequate response to 100 mg. (b) (4) Furthermore, the clinical reviewer recommends limiting the indication to third-line (refractory) atopic dermatitis based on the overall safety issues with the JAK inhibitor class. This recommendation is consistent with the JAK inhibitors place in therapy for other inflammatory conditions.[23]

The Agency's revised indication and dosage recommendations are as follows[24]:

- Cibinqo is indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics or when use of those therapies is inadvisable
- The recommended dosage of Cibinqo is 100 mg orally once daily.
    - If an adequate response is not achieved with Cibinqo 100 mg orally daily after 12 weeks, consider increasing dosage to 200 mg orally once daily. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.

The labeling for abrocitinib will communicate the risks of serious infections, mortality, malignancies, MACE, and thrombosis with a Boxed Warning. This Boxed Warning is consistent with the Boxed Warnings for other agents in the JAK inhibitor class approved for inflammatory conditions including atopic dermatitis. The risk of laboratory abnormalities (including hematologic abnormalities will be

communicated in Section 5, Warnings and Precautions and Section 2, Dosage and Administration which includes a recommended schedule for monitoring complete blood counts (CBC) and recommendations for discontinuation of therapy based on CBC. A small number of cases of retinal detachment were observed in the clinical trials and this data will be communicated in Section 6, Adverse Reactions.

Based on the data currently available, this reviewer is not recommending a REMS for the risks of abrocitinib. While the risks of abrocitinib are serious, they are similar to the risks of approved therapies in this drug class. Although one of the initial JAK inhibitors, tofacitinib, was originally approved with a REMS, the REMS was released in 2016 because the communication plan activities were completed, and assessments showed that healthcare professionals understood the key messages. Currently, no risk mitigation strategies beyond labeling are used to communicate the risks for any agent within this drug class. Previously, none of the JAK inhibitors were approved for atopic dermatitis; however, a topical formulation of ruxolitinib was approved for mild-to-moderate atopic dermatitis in September 2021. Labeling for abrocitinib will be consistent with topical ruxolitinib and the other JAK inhibitors approved for inflammatory conditions. The likely prescribing population may also be familiar with many of the risks (e.g., infections, malignancy, hematologic abnormalities) as they are similar to risks associated with conventional immunosuppressants. Labeling including a Boxed Warning and a Medication Guide should be sufficient for communicating the risks of abrocitinib.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety and proposed risk management approach for abrocitinib is similar to other agents within the JAK inhibitor class approved for inflammatory conditions including atopic dermatitis. We expect healthcare providers to be appropriately informed about the risks through labeling which includes a Boxed Warning. Additionally, some risks (e.g., infections, malignancy, hematologic abnormalities) associated with abrocitinib are similar to risks of conventional immunosuppressants which may be prescribed for moderate-to-severe atopic dermatitis. Therefore, prescribers may be familiar with these risks and the appropriate monitoring and management. At the time of this review, labeling negotiations were ongoing. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

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10.2 TABLE 1. FDA-APPROVED JAK INHIBITORS[27]

Name (generic), Approval Year	Indications[i]	Formulation	Risk Management Approaches/Boxed Warning, Medication Guide
Xeljanz and Xeljanz XR **(tofacitinib), 2012**	• Rheumatoid Arthritis • Psoriatic Arthritis • Ulcerative Colitis • Polyarticular Course Juvenile Idiopathic Arthritis • Ankylosing spondylitis	oral tablets, extended-release tablets, and oral solution	**REMS history**: Approved with REMS consisting of a Medication Guide, Communication Plan, and timetable for submission of assessments for the risk of serious infections, malignancies, lympho-proliferative disorders, increased cholesterol, and low blood cell counts. REMS was released in 2016. **Boxed Warning:** serious infections, mortality, malignancies, major adverse cardiovascular events (MACE), and thrombosis **Warnings and Precautions** (in addition to those already described in the Boxed Warning) include: gastrointestinal (GI) perforations; hypersensitivity; laboratory abnormalities (lymphocyte abnormalities, neutropenia, anemia, liver enzyme elevations, lipid elevations); need to avoid live vaccines during treatment; and risk of GI obstruction with the XR formulation **Medication Guide**
Olumiant (baricitinib), 2018	• Rheumatoid Arthritis	oral tablets	**Boxed Warning:** serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those already described in the Boxed Warning) include: gastrointestinal (GI) perforations; laboratory abnormalities (neutropenia, lymphopenia, anemia, liver enzyme elevations, lipid elevations); need to avoid live vaccines during treatment; and hypersensitivity

[i] This table does not capture the full indication statement but aims to provide a high-level overview of the diseases each JAK inhibitor is indicated to treat. See full prescribing information for more details.

			Medication Guide
Rinvoq (upadacitinib), 2019	• Rheumatoid arthritis • Psoriatic arthritis	oral capsules	**Boxed Warning**: serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those already described in the Boxed Warning) include gastrointestinal (GI) perforations; laboratory parameters (neutropenia, lymphopenia, anemia, lipids, liver enzyme elevations); embryofetal toxicity; and need to avoid live vaccines during treatment **Medication Guide**
Opzelura, ruxolitinib cream, for topical use, **2021**	• Atopic dermatitis	Topical cream	**Boxed Warning:** serious infections, mortality, malignancies, MACE, and thrombosis **Warnings and Precautions** (in addition to those already described in the Boxed Warning) include: thrombocytopenia, anemia, and neutropenia, lipid elevations **Medication Guide**
Jakafi (ruxolitinib), 2011	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host Disease • Chronic graft-versus-host disease	Oral tablets	**Warnings and Precautions** include: thrombocytopenia, anemia, and neutropenia; risk of infection; symptom exacerbation following interruption or discontinuation of therapy; non-melanoma skin cancer; lipid elevations; MACE; thrombosis; secondary malignancies
Inrebric (fedratinib), 2019	• Myelofibrosis	Oral capsules	**Boxed Warnin**g: Encephalopathy including Wernicke's **Warnings and Precautions** (in addition to those already described in the Boxed Warning) include: anemia and thrombocytopenia, GI toxicity, hepatic toxicity, amylase and lipase elevation, MACE, thrombosis, and secondary malignancies **Medication Guide**

10.3 TABLE 2: FDA-APPROVED THERAPIES FOR THE TREATMENT OF ATOPIC DERMATITIS[16,27]

Drug (Approval Date)	Indication	Dosing and Administration	Risk Management Approaches
Topical corticosteroids	Anti-inflammatory or immunosuppressant agent in the treatment of a variety of diseases	Varies	**Adverse Reactions (if systemically absorbed)** • Adrenal suppression • Cardiovascular effects (hypertension, dyslipidemia, fluid retention, and electrolyte abnormalities) • Central Nervous System and Psychiatric/Behavioral Effects • Cushingoid features • Gastrointestinal effects (peptic ulcer, dyspepsia, gastritis, ulcerative esophagitis, and abdominal distension) • Hyperglycemia • Infection • Neuromuscular and Skeletal effects • Ocular effects (increased intraocular pressure and glaucoma)
Tacrolimus 0.03% ointment and 0.1% ointment – Protopic (12/08/2000)	0.03% and 0.1% for adults and 0.03% for children aged 2 to 15 years Second-line therapy for the short term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.	Apply a thin layer to the affected skin twice daily	**Boxed Warning for Protopic and Elidel:** Long-term safety of topical calcineurin inhibitors has not been established. Rare cases of malignancy. Avoid continuous, long-term use in any age group. Not indicated in children less than 2 years of age. **Warnings and Precautions:** • Risk of Immunosuppression associated with ↑ risk of infections, lymphomas, and skin malignancies. • Avoid use on malignant or pre-malignant skin conditions • May be associated with ↑ risk of varicella zoster virus infection , herpes simplex virus infection, or eczema herpeticum • Lymphadenopathy • Sun exposure – avoid or minimize
Pimecrolimus 1% cream - Elidel (12/13/2001)	1% cream is indicated as second-line therapy for the short term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription	Apply a thin layer to the affected skin twice daily	

	treatments for atopic dermatitis, or when those treatments are not advisable.		
Crisaborole 2% ointment - Eucrisa (12/14/2016)	For topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older	Apply a thin layer to the affected skin twice daily	**Warnings & Precautions** • Hypersensitivity Reactions
Dupilumab injection - Dupixent (03/28/2017)	For the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.	Adults: Initial dose of 600 mg, followed by 300 mg every other week (Q2W) Pediatric: Dose and frequency depends on body weight	**Warnings & Precautions** • Hypersensitivity • Conjunctivitis and Keratitis • Eosinophilic Conditions • Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPIXENT • Arthralgia • Parasitic (Helminth) Infections • Avoid live vaccines
Ruxolitinib 1.5% cream - Opzelura (09/21/2021)	For the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable	Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 grams per week.	**Boxed Warning** Serious infections, mortality, malignancies, major adverse cardiovascular events (MACE), and thrombosis **Warnings & Precautions:** • Serious infections • Mortality • Malignancy and Lymphoproliferative Disorders • MACE • Thrombosis • Thrombocytopenia, Anemia, and Neutropenia • Lipid Elevations
Tralokinumab-ldrm – Adbry (12/27/2021)	For the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids.	Initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. After 16 weeks, for patients with body weight below 100 kg who achieve clear or	**Warnings & Precautions** • Hypersensitivity • Conjunctivitis and Keratitis • Parasitic (Helminth) Infections • Avoid live vaccines

		almost clear skin, a dosage of 300 mg every 4 weeks may be considered	

10.4 TABLE 3: CONVENTIONAL IMMUNOSUPPRESSANTS FOR THE TREATMENT OF MODERATE/SEVERE ATOPIC DERMATITIS[16,21,27,28]

Drug	Use (Off-Label)	Risk Management Approaches
Cyclosporine	Short-term treatment of moderate-to-severe atopic dermatitis	**Boxed Warning:** • Experienced physician • Immunosuppression/Infection/Neoplasia • Bioavailability (variable amongst products) • Skin malignancies (psoriasis patients treated with PUVA (ultraviolet light therapy) or other immunosuppressive agents) • Hypertension/Nephrotoxicity
Methotrexate	Long-term control of moderate to severe atopic dermatitis	**Boxed Warning**: (oral methotrexate) • Serious adverse reactions including death. • Severe or fatal adverse reactions: monitor for bone marrow suppression, serious infections, renal toxicity, gastrointestinal toxicity, hepatic toxicity, pulmonary toxicity, and dermatologic reactions • Hypersensitivity • Embryo-fetal toxicity
Mycophenolate mofetil	Long-term treatment of atopic dermatitis (2nd line therapy)	**REMS:** to mitigate the risk of embryofetal toxicity associated with the use of mycophenolate during pregnancy **Boxed Warning**: • Experienced physician • Serious Infections • Malignancies • Embryo-fetal toxicity
Azathioprine	Long-term treatment of atopic dermatitis (2nd line therapy)	**Boxed Warning:** • Malignancy **Warnings and Precautions:** • Gastrointestinal toxicity • Hematologic toxicity • Hepatotoxicity • Infections • *Pediatric consideration: secondary hemophagocytic lymphohistiocytosis (HLH)

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